PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference PN/4-33722A GW	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/EP2005/003664	International filing date *(day/month/year)* 07 April 2005 (07.04.2005)	Priority date *(day/month/year)* 08 April 2004 (08.04.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant NOVARTIS AG		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 17 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 11 October 2006 (11.10.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Agnes Wittmann-Regis
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Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

PCT

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/EP2005/003664	International filing date *(day/month/year)* 07.04.2005
Priority date *(day/month/year)* 08.04.2004	
International Patent Classification (IPC) or both national classification and IPC A61K38/13, A61P9/10, A61P25/00	
Applicant NOVARTIS AG	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/003664

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/003664

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-6 (all partially)

because:

☒ the said international application, or the said claims Nos. 2-6 (all partially) with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1,2,4-6 (all partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 3 (completely), 1,2,4,5,6 (partially) (= inventions 1and 2 out of 19 inventions)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	-
	No:	Claims	1-6
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-6
Industrial applicability (IA)	Yes:	Claims	1
	No:	Claims	-

2. Citations and explanations

   see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Invention 1:

Re Item III.

1. Claims 2,3,5 and 6 relate at least partially to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

2. Present claims 1 and 2 relate to the use of a product defined by reference to a desirable characteristic or property, namely the desirable property of cyclosporins to be non-immunosuppressive and cyclophilin-binding.
The claims cover the use of all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the use of the products defined by formula (A) in claim 3.

Re Item IV.

1. **Unity of inventions**

The application lacks unity of inventions as required by Article 3(4)(iii) and 17(3)(a) PCT for the following reason:

The inventions as defined above relate to the use of cyclosporin derivatives for the treatment and prevention of medical conditions ischemic brain damage, traumatic brain or spinal cord injury or stroke.

The common concept underlying the present application is that those cyclosporin derivatives prevent or ameliorate ischemic brain damage, traumatic brain or spinal cord injury or stroke.

A cyclosporin derivative, namely cyclosporin A, which prevents or ameliorates ischemic brain damage, traumatic brain or spinal cord injury or stroke is already known in the art (please see US6255280, examples 1-4 or WO9965933, see particularly the respective citations in the International Search Report).

In light of this prior art the above mentioned common concept is not novel and the problem underlying the present application can be redefined as:

The provision of additional cyclosporin derivatives for use in treatment and prevention of medical conditions ischemic brain damage, traumatic brain or spinal cord injury or stroke.

The uses of cyclosporin derivatives identified in inventions 1 and 2 are different solutions to this problem.

Due to the fact that a cyclosporin derivative, which prevents or ameliorates ischemic brain damage, traumatic brain or spinal cord injury or stroke is known in the prior art and due to the fact that no other technical feature can be distinguished which, in the light of the prior art, could be regarded as a special technical feature in the sense of Rule 13.2 PCT due to the essential differences in the primary structures of the peptides contained in these mixtures, there is no single general inventive concept underlying the plurality of claimed inventions of the present application in the sense of Rule 13.1 PCT. Consequently, the application lacks unity of invention and the different inventions are as formulated as the different subjects on the communication pursuant to Art. 17(3)(a) PCT.

Attention is drawn to the fact, that further objections concerning absence of unity of invention with respect to invention 2 may be raised, depending on the result of the respective search. In this respect, please see Item IV under Invention 2.

Re Item V.

Reference is made to the following document:

D1: WO 99/65933 A (C-CHEM AG) 23 December 1999 (1999-12-23)

2. Novelty and inventive step (Art. 33(2)(3), PCT)

2.1 It is pointed out that the present communication concerning novelty, inventive step and industrial applicability only refers to subject-matter for which an International Search Report has been established (see items III and IV).

2.2 The present invention 1 relates to the use of certain cyclosporins defined by formula (A) for the manufacture of a medicament for treating or preventing ischemic brain damage, traumatic brain or spinal cord injury or stroke.

2.3 Document D1 discloses various cyclosporin derivatives, i.a. derivatives substituted at position 3 with S-$(O)_{0-2}$-R2, which fall within the definition of cyclosporin derivatives according to formula (A) of invention 1 for use in manufacturing a medicament for treating and preventing diseases like ischemia, spinal cord injury, nerve tissue damage or infarct (page 3, lines 4-9, page 6, lines 8-26; page 8, lines 16-18).
In view of D1, subject-matter of claims 1-3,5 and 6 cannot be regarded as novel (Art. 33(2), PCT).

2.4 Independent of the above novelty objection the present invention 1 does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-3,5 and 6 does not involve an inventive step in the sense of Article 33(3) PCT for the following

reason:
The problem underlying present invention 1 is the provision of cyclosporins for the manufacture of a medicament for treating or preventing ischemic brain damage, traumatic brain or spinal cord injury or stroke.
Invention 1 claims the known cyclosporin derivatives defined by formula (A) for use in preventing or treating said diseases. The present application however contains no data which could credible support such an effect of said cyclosporin derivatives. In the absence of such data, the alleged effect is not more than a speculation. The provision of three also known assays, which could serve to test if the cyclosporin derivatives mentioned in formula (A) indeed have the desired effect, is regarded as an invitation to start a screening program, but not as a credible demonstration of a specific therapeutic use of such compounds.
In the absence of a credible demonstration that most of the cyclosporin derivatives defined by formula (A) exhibit the alleged effect, the problem of invention 1 as detailed above is regarded as not having been solved. Consequently, no inventive step can be acknowledged for subject-matter of claims 1-3,5 and 6 as far as invention 1 is concerned (Art. 33(3), PCT).

2.5 For the assessment of the present claims 2,3,5 and 6 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII.

3. Further remarks

It is noticed that claim 3 contains a line, which at the moment underlines the peptide sequence, but which should probably indicate that the peptide is a cyclic peptide.

However two small vertical lines are missing to indicate a cycle (Art. 6, PCT).

Invention 2:

Re Item III.

1. Claims 2,4,5 and 6 relate at least partially to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

2. Present claims 1-5 relate to the use of an extremely large number of possible compounds, i.e. formula (I) comprises far more than 15.000 different compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported, namely to the use of the ciclosporins mentioned as preferred ciclosporins according to claim 5 and the description on page 5.

Re Item IV.

It is pointed out that in the present case, it was first established that a search can only be carried out for a part of the claimed subject-matter of invention 2 (please see item III. 2. above), before the question of unity of inventions was considered.

1. Unity of inventions

The subject-matter defined as invention 2 in the "Invitation to Pay Additional Fees" dated 30.09.2005, lacks unity of inventions as required by Article 3(4)(iii) and 17(3)(a) PCT for the following reason:

The invention 2 as defined before relates to the use of cyclosporin derivatives according to formula (i) for the treatment and prevention of the medical conditions ischemic brain damage, traumatic brain or spinal cord injury or stroke. Of all ciclosporins falling under formula (I), the search had to be restricted to the use of the preferred ciclosporins as mentioned in claim 5 and on page 5 of the description for the reason detailed in item III above.

The common concept of these preferred ciclosporins is that those cyclosporin derivatives all fall under formula (I) and that they are used for the manufacture of a medicament for treating or preventing ischemic brain damage, traumatic brain or spinal cord injury or stroke.

Cyclosporins, namely cyclosporin A or the cyclosporin [MeVal] 4-ciclosporin, which fall under formula (I) and which prevent or ameliorate ischemic brain damage, traumatic brain or spinal cord injury or stroke are already known in the art (please see US6255280, examples 1-4 or WO9965933, or Friberg et al.,84, 241-250, see particularly the respective citations in the International Search Report).

In light of this prior art the above mentioned common concept is not novel and the problem underlying the present application can be redefined as:

The provision of additional cyclosporin derivatives for use in treatment and prevention of ischemic brain damage, traumatic brain or spinal cord injury or stroke.

The uses of cyclosporin derivatives identified in inventions 2 to 19 below are different solutions to this problem.

Due to the fact that cyclosporin derivatives, which fall under formula (I) and which prevent or ameliorate ischemic brain damage, traumatic brain or spinal cord injury or stroke are known in the prior art, and due to the fact that no other technical feature can be distinguished which, in the light of the prior art, could be regarded as a special technical feature in the sense of Rule 13.2 PCT, there is no single general inventive concept underlying the plurality of claimed inventions of the present application in the sense of Rule 13.1 PCT. Consequently, the subject-matter formerly identified as invention 2 in the "Invitation to Pay Additional Fees" dated 30.09.2005, lacks unity of invention and the different inventions are as formulated below:

1.1 Invention 2: (claims 1,2,4,5 partially)

Use of the ciclosporin mentioned in claim 5 **item (a)** for preventing or ameliorating ischemic brain damage, traumatic brain or spinal cord injury or stroke.

1.2 Invention 3: (claims 1,2,4,5 partially)

Use of the ciclosporin mentioned in claim 5 **item (b)** for preventing or ameliorating ischemic brain damage, traumatic brain or spinal cord injury or stroke.

1.3 Invention 4: (claims 1,2,4,5,6 partially)

Use of the ciclosporin mentioned in claim 5 **item (c)** for preventing or ameliorating ischemic brain damage, traumatic brain or spinal cord injury or stroke.

1.4 Invention 5: (claims 1,2,4,5 partially)

Use of the ciclosporin mentioned in claim 5 **item (d)** for preventing or ameliorating

ischemic brain damage, traumatic brain or spinal cord injury or stroke.

1.5 Invention 6: (claims 1,2,4,5,6 partially)

Use of the ciclosporin mentioned in claim 5 **item (e)** for preventing or ameliorating ischemic brain damage, traumatic brain or spinal cord injury or stroke.

1.6 Invention 7: (claims 1,2,4,5 partially)

Use of the ciclosporin mentioned in claim 5 **item (f)** for preventing or ameliorating ischemic brain damage, traumatic brain or spinal cord injury or stroke.

1.7 Invention 8: (claims 1,2,4,5 partially)

Use of the ciclosporin mentioned in claim 5 **item (g)** for preventing or ameliorating ischemic brain damage, traumatic brain or spinal cord injury or stroke.

1.8 Invention 9: (claims 1,2,4,5 partially)

Use of the ciclosporin mentioned in claim 5 **item (h)** for preventing or ameliorating ischemic brain damage, traumatic brain or spinal cord injury or stroke.

1.9 Invention 10: (claims 1,2,4,5 partially)

Use of the ciclosporin mentioned in claim 5 **item (i)** for preventing or ameliorating ischemic brain damage, traumatic brain or spinal cord injury or stroke.

1.10 Invention 11: (claims 1,2,4,5 partially)

Use of the ciclosporin mentioned in claim 5 **item (j)** for preventing or ameliorating ischemic brain damage, traumatic brain or spinal cord injury or stroke.

1.11 Invention 12: (claims 1,2,4,5 partially)

Use of the ciclosporin mentioned in claim 5 **item (k)** for preventing or ameliorating ischemic brain damage, traumatic brain or spinal cord injury or stroke.

1.12 Invention 13: (claims 1,2,4,5 partially)

Use of the ciclosporin mentioned in claim 5 **item (l)** for preventing or ameliorating ischemic brain damage, traumatic brain or spinal cord injury or stroke.

1.13 Invention 14: (claims 1,2,4,5 partially)

Use of the ciclosporin mentioned in claim 5 **item (m)** for preventing or ameliorating ischemic brain damage, traumatic brain or spinal cord injury or stroke.

1.14 Invention 15: (claims 1,2,4,5 partially)

Use of the ciclosporin mentioned in claim 5 **item (n)** for preventing or ameliorating ischemic brain damage, traumatic brain or spinal cord injury or stroke.

1.15 Invention 16: (claims 1,2,4,5 partially)

Use of the ciclosporin mentioned in claim 5 **item (o)** for preventing or ameliorating ischemic brain damage, traumatic brain or spinal cord injury or stroke.

1.16 Invention 17: (claims 1,2,4,5 partially)

Use of the ciclosporin mentioned in claim 5 **item (p)** for preventing or ameliorating ischemic brain damage, traumatic brain or spinal cord injury or stroke.

1.17 Invention 18: (claims 1,2,4,5,6 partially)

Use of the ciclosporin mentioned in claim 5 **item (q)** for preventing or ameliorating ischemic brain damage, traumatic brain or spinal cord injury or stroke.

1.18 Invention 19: (claims 1,2,4,5 partially)

Use of the ciclosporin mentioned in claim 5 **item (r)** for preventing or ameliorating ischemic brain damage, traumatic brain or spinal cord injury or stroke.

Re Item V.

Reference is made to the following document:

D2: WO 99/62540 A (NOVARTIS AG [CH]; NOVARTIS ERFIND VERWALT GMBH [AT]) 9 December 1999 (1999-12-09)

2. Novelty and inventive step (Art. 33(2)(3), PCT)

2.1 It is pointed out that the following comments concerning novelty, inventive step and industrial applicability only refer to subject-matter for which an International Search Report has been established (see items III and IV).

2.2 The present invention 2 relates to the use of [dihydro-MeBmt] 1-[gamma-MeLeu] 4-Ciclosporin for the manufacture of a medicament for treating or preventing ischemic brain damage, traumatic brain or spinal cord injury or stroke.

2.3 Document D2 is regarded as closest prior art. It *inter alia* mentions the use of [dihydro-MeBmt] 1-[gamma-MeLeu] 4-Ciclosporin for the manufacture of a medicament for treating or preventing inflammatory autoimmune diseases. The difference between D2 and present invention 2 is that both documents refer to different medical uses of the compound [dihydro-MeBmt] 1-[gamma-MeLeu] 4-Ciclosporin (D2 : autoimmune diseases; invention 2: ischemic brain damage, traumatic brain or spinal cord injury, stroke).
Further, do other cited document suggests that [dihydro-MeBmt] 1-[gamma-MeLeu] 4-Ciclosporin might also be suitable for the manufacture of a medicament for treating or preventing ischemic brain damage, traumatic brain or spinal cord injury, stroke.
Consequently, subject-matter of invention 2 as defined above is novel and inventive in view of D2 (Art. 33(2)(3), PCT.

2.4 Independent of the above comment in item 2.3, the present invention 2 does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1,2,4 and 5 does not involve an inventive step in the sense of Article 33(3) PCT for the following reason:
The problem underlying present invention 2 is the provision of a cyclosporin for the manufacture of a medicament for treating or preventing ischemic brain damage, traumatic brain or spinal cord injury or stroke.
Invention 2 claims the known cyclosporin [dihydro-MeBmt] 1-[gamma-MeLeu] 4-Ciclosporin for use in preventing or treating said diseases. **The present application however contains no data which could credible support such an effect of said cyclosporin derivatives.** In the absence of such data, the alleged effect is not more

than a speculation. The provision of three also known assays, which could serve to test if the cyclosporin derivatives mentioned in formula (A) indeed have the desired effect, is regarded as an invitation to start a screening program, but not as a credible demonstration of a specific therapeutic use of such compounds.
In the absence of a credible demonstration that [dihydro-MeBmt] 1-[gamma-MeLeu] 4-Ciclosporin exhibits the alleged effect, **the problem of invention 2 as detailed above is regarded as not having been solved**. Consequently, no inventive step can be acknowledged for subject-matter of claims 1,2,4 and 5 as far as invention 2 is concerned (Art. 33(3), PCT).

2.5 For the assessment of the present claims 2 and 4-6 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.